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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER
	6

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/393,844	HIGH ET AL.	
	Examiner	Art Unit	
	Lisa J. Gansheroff	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-9 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-9 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☒ Other: *Notice to Comply with Sequence Rules*.

DETAILED ACTION

Pending claims: 1-9

Acknowledgement is made of receipt of the Preliminary Amendment, filed 10 September, 1999, and the change of address filed 8 November, 2000.

Specification

The disclosure is objected to because of the following informalities: on pages 2 and 3, the text at the top right hand corners of the page is missing. (It looks as though the corner of each page was folded back during xeroxing.) The missing text on page 2 is any word after "to" on line 1 and any word after "these" on line 2. The missing text on page 3 includes the right side of lines 1-5 (and possibly the right end of line 6).

Appropriate correction is required.

Priority

If applicant desires priority under 35 U.S.C. 120 based upon a previously filed copending application, specific reference to the earlier filed application must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a patent, the expression "now Patent No._____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

Although Applicants have submitted a Preliminary Amendment to reference the prior applications 09/038910 and 60/040711, Applicants should provide the current status of all non-provisional applications.

In reviewing the prosecution history of the parent case 09/038910, the examiner of the instant application found the Declaration filed by one of the Applicants (Katherine A. High), dated 18 June 1999, to state that the conception of the invention and reduction to practice of the administration of Factor IX in an AAV vector was prior to November 1996. While the parent case is drawn to a method and the instant case is drawn to a composition, a composition that meets some of the limitations of the instant claims was described in a xerox of a notebook page supplied with the Declaration, and this information was thus considered when deciding whether references were prior art for the instant application.

Sequence compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

There is a paper copy of the Sequence Listing, but it is not in the proper format and there is no computer readable form of record. All sequences in the specification must be listed in the

Sequence Listing and must comply with the requirements of 37 CFR 1.821 - 1.825.

If the Sequence Listing in the instant application is identical to that of another application, the following option is also available:

Sample Request to Use Computer Readable Form from Another Application:

The following paragraph, or language having the same effect, can be used to invoke the procedures of 37 CFR section 1.821(e) in which an identical computer readable form from another application is used in a given application. The paragraph should be incorporated into a separate paper to be submitted in the given application:

The computer readable form in this application, 08/100,000, is identical with that filed in Application Number 07/999,999, filed March 1, 1988. In accordance with 37 CFR 1.821(e), please use the [first-filed, last-filed or only, whichever is applicable] computer readable form filed in that application as the computer readable form for the instant application. It is understood that the Patent and Trademark Office will make the necessary change in application number and filing date for the computer readable form that will be used for the instant application. A paper copy of the Sequence Listing is [included in the originally-filed specification of the instant application, included in a separately filed preliminary amendment for incorporation into the specification, whichever is applicable].

Any response to this Office Action which fails to meet all of these requirements will be considered non-responsive. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a). Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "isolated DNA encoding Factor IX and accompanying 5' and 3' untranslated regions". It is unclear what these are meant to be, since the claim also recites a "promoter/regulatory sequence". Is the DNA encoding Factor IX operably linked to said promoter/regulatory sequence? Is there also a promoter/regulatory sequence within said accompanying 5' untranslated region?

Claim 2 recites that the composition of claim 1 further comprises a portion of intron I. Is this intron portion part of the isolated DNA in the vector, or is it just present in the composition?

Claim 5 recites the limitation "said mutated DNA". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-3 and 6-8 are rejected under 35 U.S.C. 102(a) as being anticipated by Wiener *et al.* (WO 96/15777). Claim 1 is drawn to a composition that comprises an adeno-associated virus vector comprising inverted terminal repeats, a promoter/regulatory sequence, DNA encoding Factor IX (and indefinite 5' and 3' untranslated regions), and a transcription termination signal. Claims 2 and 3 recite limitations about an intron, and claims 6-8 recite limitations about a carrier, the promoter sequence, and the transcription termination signal.

Wiener *et al.* teach an adeno-associated viral vector that comprises two adeno-associated inverted terminal repeats (ITR), DNA encoding Factor IX with a truncated intron under the control of the cytomegalovirus regulatory sequence and with an SV40 poly A sequence (a transcription termination signal). Since the composition is described as used for treatment of hemophilia, inherent in the composition is that the carrier is pharmaceutically acceptable. See Figures 14 and 15 and pages 1, 6-8, 19, and 20 of the reference.

Claims 1-3 and 6-8 are rejected under 35 U.S.C. 102(e) as being anticipated by Wilson *et al.* (U.S. Patent 5,866,552).

Wilson *et al.* teach a composition that comprises an AAV (adeno-associated virus) vector that comprises inverted terminal repeat sequences, a promoter/enhancer which can be the cytomegalovirus immediate early promoter/enhancer, a poly A sequence from SV-40 (for transcription termination). Wilson *et al.* teach that a gene in the vector can be a therapeutic gene which encodes a desired gene product, and teach that the gene can encode factor IX. See

columns 4, 5, and 6 of the reference. Wilson *et al.* also teach that the gene can be introduced into muscle, and thus inherent in the method of Wilson *et al.* is the use of any muscle-specific promoter/regulatory sequence.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3 and 6-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wiener *et al.*, as applied to claims 1-3 and 6-8, and further in view of Crabtree *et al.* (U.S. Patent 5,834,266).

Crabtree *et al.* teach that an adeno-associated viral vector can be in a kit. See claim number 230 and columns 9 and 10 of Crabtree *et al.* Crabtree *et al.* do not teach a kit with DNA encoding Factor IX.

At the time of the invention of the instant application, one of ordinary skill in the art would have been motivated to prepare a pharmaceutical composition comprising a vector with DNA encoding Factor IX to treat hemophilia, and since kits are commercially valuable and convenient ways of storing compositions and supplying them to other researchers, one would have been motivated to produce a kit comprising the vector and instructions for using the vector. It would have been obvious to the ordinary artisan to combine the teachings of Wiener *et al.* with the teachings of Crabtree *et al.* It also would have been obvious to include instructions in the kit so that another researcher would know how to use the composition. Success would have been expected in the preparation of the kit.

Claims 1-3 and 6-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Skulimowski *et al.*, and further in view of Kurachi *et al.* (cited in the specification), Webster *et al.*, Theill *et al.*, Kaufman, and Roman *et al.*

Skulimowski *et al.* teach AAV vectors and teach reasons why these vectors are advantageous over other vectors for gene therapy. The vectors comprise two AAV inverted terminal repeats, a cytomegalovirus regulatory promoter sequence (CMV), and a gene encoding a protein to be expressed. (See pages 3-4 and Fig. 2). Skulimowski *et al.* do not specifically teach Factor IX.

Kurachi *et al.* teach that portions of intron I of Factor IX enhance expression (see Figure

2, Table II, and first page). Kurachi *et al.* also teach that a deficiency of Factor IX results in hemophilia B, an abnormal bleeding disorder. Kurachi *et al.* do not teach adeno-associated vectors.

Webster *et al.* teach that adeno-associated virus vectors (AAV) can express genes under skeletal-muscle specific promoters such as the actin promoter. See columns 16 and 21. Webster *et al.* do not teach Factor IX.

Theill *et al.* teach that the creatine kinase promoter or the cytomegalovirus promoter (CMV) can be used in a vector, such as an adeno-associated vector, that is to be injected into muscle tissue (see column 18, lines 29-51). Theill *et al.* do not teach Factor IX.

Kaufman teaches a variety of vectors for expression in mammalian cells. Kaufman teaches transcription termination and polyadenylation and teaches that efficient signals for polyadenylation from SV40 are commonly used (pages 502- 503). Kaufman does not teach adeno-associated virus vectors or Factor IX.

Roman *et al.* teach a retroviral vector that comprises DNA that encodes Factor IX expressed from the cytomegalovirus promoter. The vector was put into myoblasts, and Factor IX was expressed in the myoblasts in culture and is expressed in vivo when the myoblasts are put into animals. Roman *et al.* also teach that muscle tissue is an abundant organ whose cells are susceptible to gene transfer methods and are easily accessible for biopsy. Roman *et al.* also teach that expressing Factor IX in muscle might be an approach to treating hemophilia. See abstract, page 250: right column, page 251: Results section and Fig. 1, page 252: right column, page 253, page 255: left column, and the first paragraph of the Discussion on pages 255-256. Roman *et al.* do not teach a portion of an intron or adeno-associated virus vectors.

At the time of the invention of the instant application, one of ordinary skill in the art would have been motivated to prepare a composition to put Factor IX-encoding DNA into myoblasts for therapeutic delivery to hemophilia patients, since Roman *et al.* teach the expression of Factor IX in myoblasts from a retroviral promoter. One would have been motivated to use adeno-associated vectors for their advantages taught by Skulimowski *et al.*, and one would have been motivated to use either a cytomegalovirus promoter or a muscle-specific promoter such as those taught by Webster *et al.* and Theill *et al.* One would have been motivated to follow the teachings of Kurachi *et al.* regarding the inclusion of a portion of intron 1 in the vector in order to enhance expression. It would have thus been obvious to the ordinary artisan to combine the teachings of these references. It would also have been obvious to prepare a kit containing the vector and instructions, since a kit is a convenient way to store reagents and to supply reagents to other researchers. Since the claims are only drawn to a composition and not to a method of treatment, success would have been expected in the preparation of the composition.

Allowable Subject Matter

Claims 4 and 5 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims, and if claim 5 is rewritten to overcome the rejection under 35 U.S.C. 112 of claim 5. The invention of these claims is deemed allowable over the prior art of record or any combination thereof. The prior art of record does not teach or suggest a an adeno-associated virus vector comprising a DNA encoding Factor IX that is mutated and rendered incapable of

binding to collagen IV. The closest prior art teaches the a mutation in Factor IX that inhibits binding to collagen IV (Cheung *et al.*, 1996), and the prior art teaches adeno-associated vectors (see art rejections of the other claims above), but the Examiner could not find a reasonable motivation in the prior art for putting into an adeno-associated vector a DNA encoding Factor IX with said mutation. Thus, the prior art does not anticipate the claimed invention of claims 4 and 5 of the instant application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa J. Gansheroff whose telephone number is (703) 605-1203. The examiner can normally be reached 9 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott can be reached on (703) 308-4003. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242 for regular communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst Dianiece Jacobs whose telephone number is (703) 305-3388 or to the receptionist whose telephone number is (703) 308-0196.

LG
December 1, 2000

REMY YUCEL, PH.D
PRIMARY EXAMINER